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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,026	08/18/2006	Nobuhiro Oikawa	OIKAWA1	5830

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,026	OIKAWA ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/06/2010 has been entered.

Status of the Claims

2. The amendments filed 1/12/2010 and 2/06/2010 were entered.

Response to Arguments

3. Applicants' arguments, filed 1/12/2010 and 2/06/2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. **Claims 1-3 and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention**.

6. Instant claim 1, in defining Q, recites that "Q is a group of formula 2… wherein the group may be substituted with ***one or two*** same or different substituents W" and then, further

states that "Q is optionally substituted by ***at least one*** substituent W". The claim language renders the claim indefinite because it is unclear whether Q can be substituted by, ***at the most***, two substituents which are W, or whether Q can be susbstituted by more than two substituents which are W. This uncertainty is further exacerbated by claim 3, which recites Q may be substituted "with one to three same or different substituents W". As such, one of ordinary skil in the art would not be reasonably able to ascertain the metes and bounds of the claim scope. Claims 1 and 3 are rejected as indefinite. The dependent claims 2 and 6-11, which fail to clarify the meaning of the indefinite language, are also rejected.

7. Additionally, claim 3 recites the limitation the compound of claim 1 wherein "R2… [is] selected from a hydrogen atom". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **Claims 1-3 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the elected compound species and those embodied by the instant Specification, is not considered enabled for the other compound species encompassed by Formula 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims**.

10. The standard for determining whether the Specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? As recognized by the court in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), that is still the standard to be applied. Determination of undue experimentation in the instant case is discussed below:

11. **Nature of the Invention**: As stated in MPEP 2164.05(a), "[t]he initial inquiry" for determining whether the Specification is enabling "is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains." In the instant case, the claimed invention pertains to compounds of Formula 1 which are alleged by the Specification to act as Raf inhibitors.

12. **The State of the Prior Art and the Relative Skill of those in the Art**: As stated in MPEP 2164.05(a), "[t]he state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains" and, as stated in MPEP 2164.05(b), "[t]he relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed."

13. As discussed above, the instantly claimed invention pertains to compounds of Formula 1 which are alleged by the Specification to act as Raf inhibitors. At the time the instant application was filed, it would have been known by those of ordinary skill in the art that - due in large part to the strict requirement of complementarity between a compound and its corresponding binding site on a target receptor or enzyme - compounds, in the vast majority of cases, demonstrate a

remarkably high correlation between their structure, specificity and ability to produce a pharmacological effect. At the same time, it would have also been generally assumed that two compounds with similar chemical properties would exhibit similar biological effects. Thus, given a series of compounds that are shown to exert an activity of interest (or given a target of interest), the ordinarily skilled artisan would have expected that a limited genus of related compounds (e.g., compounds exhibiting near equal molecular shapes and volumes, approximately the same distribution of electrons, and similar physical properties such as hydrophobicity, etc) would interact with the given target to elicit a related biological response.

14. Accordingly, at the time the invention was made, the relative skill of those in the art tasked with identifying compounds exerting an activity of interest would have been high, as the ordinarily skilled artisan would have had, at minimum, a Ph.D. and experience with screening techniques including computer assisted virtual screening techniques such as ligand-based and structure-based design methods. Deciding which technique to use would have been determined by the skilled artisan's knowledge regarding the compound and target of interest. Ligand based drug design relies on knowledge of a compound or compounds of interest (i.e., ligands) to derive new compounds that will, in theory, similarly interact with the target of interest to elicit the activity of interest. Conversely, structure based drug design relies on knowledge of the three dimensional structure of the target of interest (i.e., receptor, ion channel, or enzyme) to derive new compounds that will, in theory, interact with the target of interest to elicit the activity of interest. In either case, the compounds derived from these techniques (applied alone or in combination) are then subjected to *in vitro* testing for validation.

15. **The Level of Predictability in the Art**: Once a compound has been identified by ligand based and/or structure based drug design methods as potentially binding to the target molecule, it must be evaluated. However, as discussed by *Anderson* (Chem and Biol 10:787-797, 2003), "it is important to consider that the ranking assigned by the scoring function is not always indicative of a true binding constant, since the model of the target:ligand interaction is inherently an approximation. Usually, several molecules which scored well during the docking run are evaluated in further tests since even the top scoring molecule could fail in vitro assays… Finally, leads are brought into the wet lab for biochemical evaluation" (Page 794, Column 1). By that point, as noted by *Thiel* (Nature Biotechnol 2:513-519, 2004), "libraries are small and hit rates are on the order of one in ten" (Page 517, Column 2). This low level of predictability is not surprising considering that even minor structural changes can, and frequently will, drastically alter or eradicate a parent compound's ability to modulate the activity of a specific receptor or enzyme. Indeed, modifying even a single atom in a compound can dramatically change the compound's overall structure and - even though complementarity in one portion of the compound might be improved by the chemical revision - the overall binding or activity might be severely compromised.

16. **The Amount of Direction Provided by the Inventor / Existence of Working Examples**: The amount of direction provided by the Applicant is considered to be determined by the Specification and the working examples. In the instant case, the Specification discloses various compound species which are Raf inhibitors (Pages 324-325, Tables 4-1 to 4-3). However, only 8 of the tested compounds are within formula 1 (i.e., compounds 4, 30, 36, 57, 95-96, 104 and 119).

17. **Scope or Breadth of the Claims**: As stated in MPEP 2164.01(c), "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the ***entire*** scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use" (emphasis added). Thus, as stated in MPEP 2164.08, "[t]he focus of the examination inquiry is whether ***everything*** within the scope of the claim is enabled" (emphasis added). Indeed, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the ***full scope*** of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993) (emphasis added).

18. At the same time, however, it is also recognized that not ***everything*** necessary to practice the invention need be disclosed. Nor is it necessary that an Applicant test ***all*** the embodiments of his invention. *In re Angstadt*, 537 F.2d 498 (CCPA 1976) (emphasis added). In fact, as stated by the court in *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991), a patent need not teach, and preferably omits, what is well known in the art.

19. Accordingly, for purposes of enablement, the relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate in scope with the protection sought by the claims. Thus, while "a patent application is entitled to claim his invention generically" it is necessary that "he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims". *Amgen, In.c, v. Chugai Pharmaceutical Co., Ltd.* (Fed. Cir. 1991). As noted by the court in *In re Fisher*, 427 F.2d 833 (CCPA 1970), the scope of enablement must bear a "reasonable correlation" to the scope of the claims. See also *Ak Steel Corp. v. Sollac*, 344 F.3d 1234 (Fed. Cir. 2003) and *In re*

Moore, 439 F.2d 1232 (CCPA 1971). As stated in MPEP 2164.08, resolution of this concern requires two stages of inquiry: "[t]he first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claim without undue experimentation".

20. As to the first inquiry, as discussed above, the claims are drawn to compounds of Formula 1, which are alleged by the Specification to act as Raf inhibitors. Considering that Formula 1 encompasses hundreds of millions of compound species, and potentially billions of compound species, it is evident that the claims are broad. Yet, as discussed above, the instant Specification discloses only 8 compound species encompassed by Formula 1 as recited by the claims which exhibit Raf inhibiting activity. As such, the claim is extremely broad with respect to the disclosure.

21. The second inquiry is discussed in detail below.

22. **Amount of Experimentation Necessary**: In view of all of the foregoing, at the time the invention was made, it would have required undue experimentation to practice the entire scope of the invention as claimed. As discussed above, the claims are drawn to compounds of Formula 1, which are alleged by the Specification to act as Raf inhibitors. Since identifying ***any*** compound which is capable of modulating the activity of a specific receptor, ion channel, or enzyme is extremely complex, the nature of the instant invention considered to be one of extreme complexity. In the instant case, this complexity is exacerbated by the broadness of Formula 1 with respect to the disclosure since Formula 1 encompasses hundreds of millions of compound species, and potentially billions of compound species, whereas the instant Specification discloses

only 8 such compound species exerting the disclosed activity. Although the relative skill of those in the art to which the invention pertains is high, the state of the art and unpredictability within the art is such that even the most talented artisan (armed with screening techniques including computer assisted virtual screening techniques such as ligand-based and structure-based design methods) could not reasonably predict which of the hundreds of millions of compounds encompassed by Formula 1 would exert the alleged activity based on the limited disclosure of 8 active compounds. Although the skilled artisan would have known that certain chemical modifications to the disclosed compounds may predictably provide structurally related compounds having similar activity, the skilled artisan would have also known that even minor structural changes can, and frequently will, drastically alter or eradicate a parent compound's ability to modulate the activity of a specific receptor or enzyme. Thus, in order to identify usable compounds of Formula 1, the skilled artisan (at minimum) would have to carry out ligand based drug design methods using the 8 disclosed compounds as a starting point and, assuming the structure of the target was known, combine the findings with data derived from structure based drug design methods to arrive at a small library of "lead" compounds believed to possess the activity of interest. The skilled artisan would then synthesize lead compounds that are within Formula 1 for *in vitro* testing. At this point, however, even "the top scoring molecule could fail in vitro assays" (Page 794, Column 1) and "hit rates are on the order of one in ten" (Page 517, Column 2). Thus, it is highly unpredictable whether any compound within the subgenus of compounds of Formula 1 identified by rational drug design based on the instant disclosure would, in fact, be usable. Whether the other compounds of Formula 1 (i.e., those not identified by rational drug design based on the instant disclosure) would be usable is even less predictable.

As such, the only way to ascertain which of the hundreds of millions, and potentially billions, of claimed compounds encompassed by Formula 1 are usable based on the limited disclosure would require undue experimentation. That is, the only way one skilled in the art is enabled to use the entire scope of the claim based on the instant disclosure entails undue experimentation.

23. To overcome this rejection, Applicant should narrow the scope of the claims such that they bear a reasonable correlation with the disclosure. In particular, the definitions of R^1-R^6, Z^1-Z^2, and W should be narrowed to bear a reasonable correlation with the disclosure.

Claim Rejections - 35 USC § 103

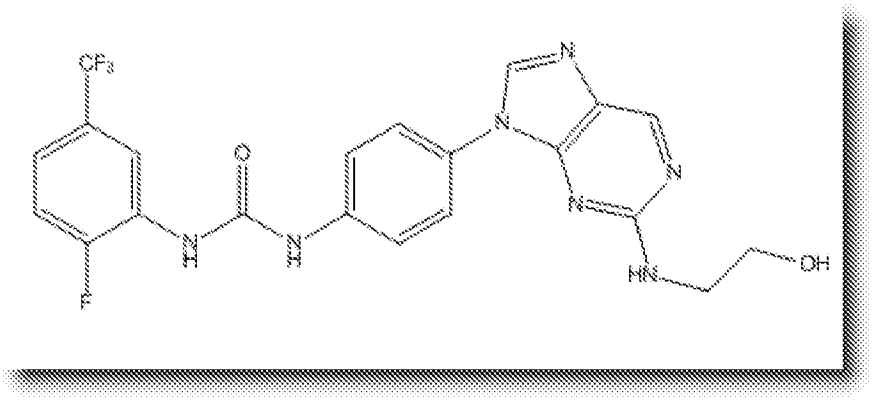
24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

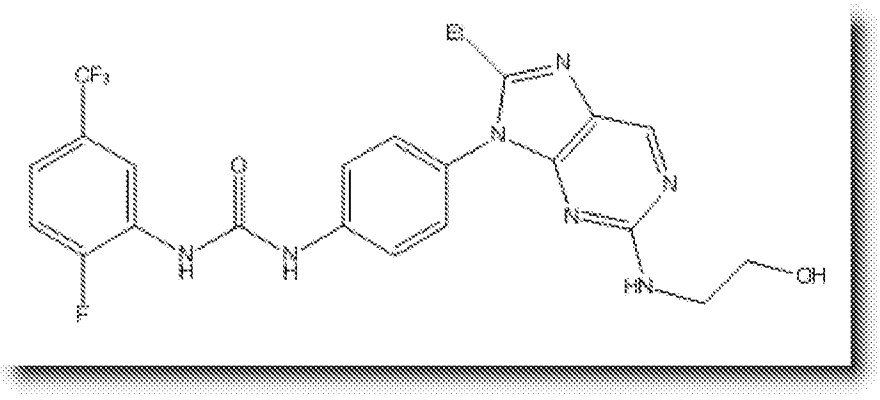
25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. **Claims 1-3 and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Adams et al* (WO 2003/029209).**

27. Instant claim 1 is drawn to a compound of formula 1 which encompasses the following compound species

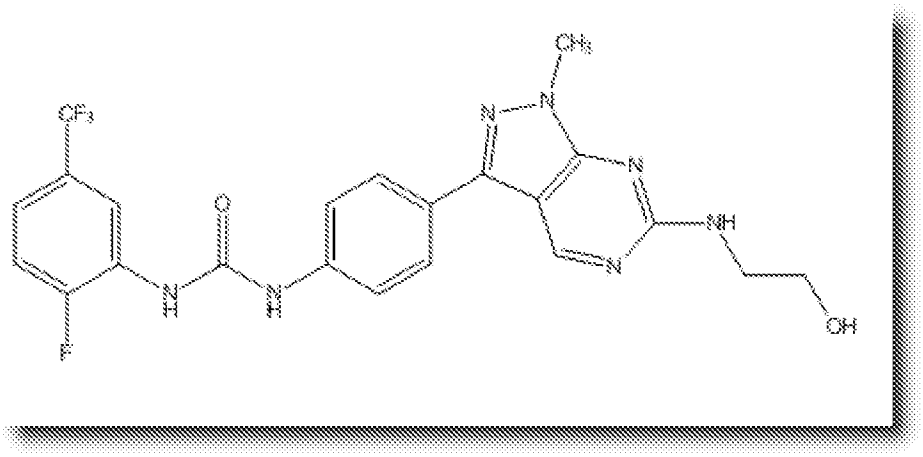


(**Species 1**) wherein, in formula 1, R^1 is H; R^2 is a C_1 alkyl substituted with halogen atoms; R^3 and R^4 are H; R^5 is a halogen atom; Z^1 and Z^2 are H; R^6 and R^7 are H; Q is Formula 2 wherein Y^1 is hydrogen and W is –NRaRb wherein Ra is H and Rb is a C_2 alkenyl group substituted with Y^3 wherein Y^3 is -ORz and Rz is H; and



(**Species 2**) wherein, in formula 1, R^1 is H; R^2 is a C_1 alkyl substituted with halogen atoms; R^3 and R^4 are H; R^5 is a halogen atom; Z^1 and Z^2 are H; R^6 and R^7 are H; Q is Formula 2 wherein Y^1 is C_2 alkenyl and W is –NRaRb wherein Ra is H and Rb is a C_2 alkenyl group substituted with Y^3 wherein Y^3 is –ORz and Rz is H

28. *Adams et al* teach the following compound species



which is disclosed as an inhibitor of TIE-2 kinase, VEGFR-2 kinase, and VEGFR-3 kinase.

29. The compound disclosed by *Adams et al* differs from the instantly claimed compounds species in two ways: (1) the arrangement of nitrogen atoms within Q; and (2) the substitution of Q with Y wherein Y is a methyl group as compared to no substitution or substitution with an ethyl group.

30. As stated by MPEP 2144.09:

> A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979).

. Furthermore:

> Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

31. In the instant case, the prior art compound taught by *Adams et al* is structurally similar to the instantly claimed compounds. Furthermore, any subtle differences that may stem from the shift of nitrogen atoms within the ring taught by *Adams et al* or the addition or substraction of a the same chemical group (i.e, -CH_2) to arrive at the instantly claimed are irrelevant since the MPEP 2144.09 states "[c]ompounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

32. Thus, in view of *In re Payne* and *In re Wilder*, a *prima facie* case of obviousness exists between the claimed compound species and the structurally similar prior art compound species expected as having similar properties. As such, instant claims 1-3 and 6-7 are rejected as *prima facie* obvious.

33. Instant claim 9 is drawn to a pharmaceutical composition comprising the compound of claim 1 as an active ingredient. Adams et al specifically teach "compositions and medicaments" (Page 1, Line 6) of the compound species which encompasses a pharmaceutical composition comprising the compound as an active ingredient. As such, instant claim 9 is also rejected as *prima facie* obvious.

34. Instant claims 8 and 10-11 are drawn to the compound of claim 1 or compositions (i.e., agents) which has "Raf inhibiting effect and angiogenesis inhibiting effect and is used for treating cancer" etc (claim 8); which is a Raf inhibitor (claim 10); or which is "for a disease selected from cancer" etc (claim 10). As discussed above, the compound and compositions thereof are prima facie obvious in view of the prior art. However, the prior art does not disclose the compounds as (1) Raf inhibitors / angiogenesis inhibitors or (2) for the treatment of the recited disease conditions. As to (1): while it is acknowledged that the discovery of a new use for an old composition or structure based on unknown properties of the structure might be patentable to the discoverer as a process of using (See *In re Hack*, 245 F.2d 246 (CCPA 1957), as stated in *In re Papesch*, 315 F.2d 381 (CCPA 1963), "[f]rom the standpoint of patent law, a compound and all its properties are inseparable". As to (2): Applicant is advised that use limitations within product claims do not carry patentable weight. Accordingly, claims 8 and 10-11 are rejected for the same reasons as applied to claim 1 discussed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Supervisory Patent Examiner, Art Unit 1628